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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/509,775	03/31/00	FUJITA J	053466/0277

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EXAMINER	
DAVIS,N	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 09/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/509,775	Applicant(s) FUJITA, JUN	
	Examiner Natalie A. Davis	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Group Art Unit examiner of the application **has been changed**. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Dr. Natalie A. Davis**.

Applicant's election with traverse of Group I, claims 1-5 and 16-17 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-5 and 16-17 are being examined as belonging to the elected Group II, while claims 6-15 and 18-24 are withdrawn from examination as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement filed 05 July 2000 has been considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Recitation of "stringent condition" is indefinite as the specification only gives a non-limiting example. This rejection may be obviated if the conditions were incorporated into the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-5, and 15-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising an amino acid sequence from Ala at position 14 to Gly at position 226 and from Met at position 1 to Gly at position 226 of SEQ ID NO: 2 and having the biological activity of gankyrin, where activity is limited to colony forming ability, carcinogenicity, and suppression of tumorigenicity, does not reasonably provide enablement for comprising an amino acid sequence, with modifications such as deletions, additions, and /or substitutions, from Ala at position 14 to Gly at position 226 and from Met at position 1 to Gly at position 226 of SEQ ID NO: 2, gankyrin and a signal-added polypeptide and a fusion polypeptide comprising an amino acid sequence from Ala at position 14 to Gly at position 226, which have the biological activity of gankyrin beyond the limitations mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a polypeptide comprising an amino acid sequence, with modifications such as deletions, additions, and /or substitutions, from Ala at position 14 to Gly at position 226 and from Met at position 1 to Gly at position 226 of SEQ ID NO: 2, which have the biological activity of gankyrin. The claims are further drawn to a signal-added polypeptide and a fusion polypeptide comprising an amino acid sequence from Ala at position 14 to Gly at position 226, which have the biological activity of gankyrin.

The specification discloses that the invention encompasses a gankyrin polypeptide that is substantially identical to SEQ ID NO:2, in which 2 or more or 30 or less amino acids are deleted, added, or substituted (page 13). The disclosure further indicates that the modified polypeptides differ in amino acid sequence, molecular weight, isoelectric point, or presence or form of sugar chains and are included in the invention as long as they have the activity substantially equivalent to the gankyrin polypeptide, wherein substantially equivalent means carcinogenicity is equivalent in property (page 14). The disclosure also states that the invention may comprise a polypeptide, in which a signal sequence has been added (page 3) and a fusion polypeptide comprising the invention and another polypeptide or peptide, such as hemaglutinin, FLAG and the like (page 4 and 22).

The instant disclosure fails to meet the enablement requirement for the following reasons:

There are many modified polypeptides, that may result from the modification via deletion, addition, and substitutions of amino acids of SEQ ID NO: 2 that may or may not perform the same biological functions. It would require the experimentation of numerous modified polypeptides to assay for modified, signal-added, and fusion polypeptides that retain the colony forming ability, carcinogenicity, and suppression of tumorigenicity activities of gankyrin. Furthermore, has not enabled all of these types of modified proteins because it has not been shown that modified polypeptide are capable of functioning as that which is being disclosed. The specification defines gankyrin activity as transcriptional, cell growth inhibiting, and apoptosis inducing (page 22). Furthermore, the disclosure exemplifies gankyrin biological activity in Example 4 (page 55-58), but does not provide any guidance or exemplification of biological activity beyond colony forming ability, carcinogenicity, and suppression of tumorigenicity in any modified, signal added, or fusion protein. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to any modified signal-added, and fusion polypeptides of SEQ ID NO: 2 with the biological activity of gankyrin. One of ordinary skill in the art would not know how to select for proteins with gankyrin activity beyond what has been exemplified. In addition, there is no guidance or exemplification of a signal-added peptide or a fusion peptide that functions as contemplated. Thus, one of ordinary skill in the art would not know how to make the polypeptide as claimed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure that modified polypeptides of SEQ ID NO. 2 retain the biological activity of gankyrin. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims, the absence of working examples, and the undue burden to one of ordinary skill in the art to assay for modified polypeptides that retain the biological activity gankyrin, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang, et al., (1995), Jamsa, et al., (1995), and Kato, et al. (Sagami Chemical Research Center, JP 9-75085, 1997). The elected claims are drawn to a signal-added peptide and a fusion polypeptide according to claim 1.

Zhang et al., teach Nus and lambda Q glutathione S-transferase fusion proteins, wherein the fusion proteins were purified under non-denaturing conditions using affinity chromatography on glutathione agarose. Jamsa, et al. teach the addition of a signal peptide to beta-lactamase so the protein may be secreted into culture medium and purified under non-denaturing conditions. Zhang, et al., and Jamsa, et al. do not teach to use a polypeptide comprising Ala at position 14 to Gly at position 226 and Met at position 1 to Gly at position 226 of SEQ ID NO: 2 and having the biological activity of gankyrin. However, Kato, et al. teach a polypeptide comprising an amino acid sequence from Met at position 1 to Gly at position 226 of SEQ ID NO: 2. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Zhang, et al., Jamsa, et al., and Kato, et al. to make a signal-added and fusion polypeptide. One of ordinary skill in the art would have been motivated to make and use the claimed polypeptides because of the reasonable expectation of success based on well known and accepted methods in the art of how signal-added may be used to secrete polypeptides to desired locations and for purification purposes and fusion proteins may be used in the purification of polypeptides.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1, 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato, et al., (Sagami Chemical Research Center, JP 9-75085, 1997). The claims are drawn to a polypeptide comprising an amino acid sequence, with and without modifications such as deletions, additions, and /or substitutions, from Ala at position 14 to Gly at position 226 of SEQ ID NO: 2 and having the biological activity of gankyrin. The claims are further drawn to a to a polypeptide comprising an amino acid sequence, with and without modifications such as deletions, additions, and /or substitutions, from Met at position 1 to Gly at position 226 of SEQ ID NO: 2, having the same biological activity. The claims are further drawn to a polypeptide that is encoded by a DNA capable of hybridizing under stringent conditions to a sequence of SEQ ID NO: 1 and gankyrin activity.

Kato, et al. teach the polypeptide comprising an amino acid sequence from Met at position 1 to Gly at position 226 of SEQ ID NO: 2. Since the amino acid sequence is identical to the claimed SEQ ID NO: 2, it is inherent that the polypeptide has the same biological activity of gankyrin. Kato, et al. further teach a polypeptide that is encoded by SEQ ID NO: 1. Since the DNA sequence is identical to the claimed sequence, it is inherent that the polypeptide is capable of hybridizing under stringent conditions to DNA of SEQ ID NO: 1 and possesses gankyrin activity.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, Ph.D.
September 6, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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